Heart Sci J 2022; 3(3):17-24

Contents list available at www.heartscience.ub.ac.id

Heart Science Journal

Journal Homepage : www.heartscience.ub.ac.id

Original Article

The Effect of HbA1C Variability and Lipid Profile on Carotid Intima-Media Thickness and Flow-mediated Dilatation in Children and Adolescents with Type 1 Diabetes Mellitus

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ARTICLE INFO

Keywords:
HbA1c Variability;
Lipid Profile;
Carotid Intima-Media Thickness;
Flow-Mediated Dilation;
Type 1 Diabetes Mellitus.

ABSTRACT

Background: Type 1 Diabetes Mellitus (T1DM) is one of the most significant factors contributing to the increased risk of cardiovascular diseases. The increase in cardiovascular diseases itself is triggered by atherosclerosis. Atherosclerosis can be detected early through carotid intima-media thickness (CIMT) and flow-mediated dilation (FMD) examination. The result of CIMT and FMD can be affected by several factors, such as HbA1c variability and lipid profile.
Objectives: This study aimed to determine the influence of HbA1c variability and lipid profile on CIMT and FMD levels found in pediatric patients with T1DM treated at Saiful Anwar General Hospital of Malang.
Methods: The study utilized a cross-sectional design that included 82 participants with Type 1 Diabetes Mellitus who were routinely treated at the pediatrics outpatient clinic in Saiful Anwar General Hospital of Malang from January to July 2019 and December 2021 to January 2022 and were willing to undergo CIMT and FMD examinations which are then taken for lipid profile and serial HbA1c tests. At least six HbA1c measurements within 18 months were included. HbA1c Variability Score (HVS), HbA1c-coefficient variation (HbA1c-CV), and HbA1c-standard deviation (HbA1c-SD) were used to evaluate variability.
Results: There was no significant correlation between HDL (ρ=-0,029; p=0,796), LDL (ρ=-0.213; p=0.055), TG (ρ=-0.179; p= 0.107), and total cholesterol (ρ=-0.182; p= 0.101) with FMD according to the test results. There was a positive correlation amongst LDL (ρ=0,318; p=0,004) and total cholesterol levels (ρ=0,230; p=0,038) with IMT. The correlation coefficient between HbA1C variability and FMD as evaluated by HVS was -0.498 (ρ =0.000; p=0.05), equal to the value that serves as the correlation coefficient between HbA1c-SD (ρ=-0.467; p=0.000) and HbA1c-CV (ρ =-0.400; p=0.000). Furthermore, there is a significant positive correlation between IMT and HbA1c variability using HVS (ρ= 0.455; p = 0.000), HbA1c-SD (ρ= 0.434; p=0.000), and HbA1c-CV (ρ= 0.325; p=0.003). The linear regression analysis revealed that the three variables with the greatest influence on FMD were HVS (R = 0.398), LDL (R = 0.316), and HbA1c-SD (R = 0.293). The three most impactful variables on IMT were HVS (R = 0.468), LDL (R = 0.268), and total cholesterol (R = 0.198). It is known that by using this model, the combination of HbA1c variability and lipid profile contributes to 25.1% on FMD and 34.5% on IMT.
Conclusion: Variability of HbA1c and lipid profile (LDL and total cholesterol) has effects on increasing the CIMT levels and decreasing the FMD of the brachial artery in children with T1DM.

1. Introduction

Diabetes mellitus (DM) has become one of the most common non-transmitted diseases in the world. International Diabetes Federation (IDF) estimated that 425 million people worldwide were affected in 2017. IDF also predicted that by 2045, the number of people affected by DM might reach 629 million. Meanwhile, there was an increasing case of DM in Indonesia from 6.9% to 8.5% back in 2018.[1]

T1DM is the most common type of diabetes found in children and adolescents. It is caused by the destruction of pancreatic beta cells as a result of the autoimmune or idiopathic process, resulting in an absolute insulin deficiency. The number of T1DM cases in children and adolescents keeps increasing these days. The IDF estimated that there are 78,000 children worldwide who tend to develop T1DM each year. According to IDF, T1DM is estimated to affect up to 1.1 million children and adolescents worldwide, and each year 133 children and adolescents are newly diagnosed with T1DM.[2] According to the Indonesian Paediatricians Association's (IDAI) registration data on 2012,

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https://doi.org/10.21776/ub.hsj.2022.003.03.4
Received 9 March 2022; Received in revised form 30 April 2022; Accepted 15 June 2022
Available online 30 July 2022

the case of T1DM ranges from 0.2 to 0.42 per 100,000 children per year.[3]

T1DM develops through an autoimmune process. It involves an inflammation reaction where there is damato on pancreatic beta cells within the islets of Langerhans caused by the auto-reactivation of pro-inflammatory cytokines. The damage to pancreatic beta cells results in insulin insufficiency. That condition triggers lipolysis. Lipolysis happens when triglycerides in adipocyte cells break down into free fatty acids, which then trigger the release of atherogenic lipoproteins such as VLDL, LDL, and IDL; it also results in the inhibition of HDL. The entire process is what caused atherosclerosis to take place.[4]

The increasing inflammation in patients with DM might also cause by the variability of glycaemic blood levels.[5] According to early studies, glycaemic variability in patients with T1DM contributed to the increase in inflammatory C-Reactive Protein (CRP), total antioxidant capacity (TAOC), and also soluble intracellular adhesion molecule 1 (sICAM1), which is a sign of oxidative stress and inflammation in the nendothelium6 Blood glucose fluctuation, both short- and long-term, has been linked to an increased risk of cardiovascular morbidity and mortality.[7]

Subclinical atherosclerosis can be detected early in a population of people at risk for cardiovascular issues, such as diabetes mellitus. These tests can be utilized as a reference for primary prevention of cardiovascular problems and reclassification for groups of people at rare risk, mainly on groups of individuals with low or moderate risk of future cardiovascular complications. The CIMT and FMD have been frequently used to detect subclinical atherosclerosis.8 Based on those mentioned above, the researchers conducted a study to determine the influence of HbA1C variability and lipid profile on CIMT and FMD found in children and adolescents with T1DM. The latter was treated at Saiful Anwar General Hospital of Malang.

2. Materials and Method

2.1 Study Sample

This study was conducted using a cross-sectional method to determine the effect of HbA1c fluctuation and lipid profile on CIMT and FMD values. All the procedures performed in this study were approved by The Committee of Research Ethics, Faculty of Medicine, Brawijaya University (No. 400/214/k.3/302/2018). The 82 research subjects were enrolled from January to July 2019 and December 2021 to January 2022. The recruitment process was conducted using the consecutive sampling approach in which each patient who met the inclusion criteria was carefully selected. All subjects were given a complete evaluation consisting of blood count, lipid profile, renal and liver function tests, and serial HbA1c measurement within 18 months. Several measures were taken from the medical record, then followed the clinical examination of CIMT and FMD. This study was conducted in the Paediatric Endocrinology and Cardiovascular Department outpatient clinic at Saiful Anwar General Hospital of Malang, Indonesia.

There were some criteria applied to the inclusion of patients with T1D. The criteria are as follow: patients who have been diagnosed with T1D, patients who are between the age of 3 and 18, and patients whose parents/guardian had given written consent to participate in the study; all information regarding patients' participation was disclosed beforehand, so parents/guardian were well-informed. On the other hand, some criteria applied to the exclusion of patients, meaning that if patients had any of the following criteria, they were excluded as participants in this study. The exclusion criteria are as follows: local and systemic infections, liver dysfunction, decreased renal function, malignancy, and anemia (hemoglobin levels 11 g/dL, history of Vitamin D supplementation during the past three weeks, amlodipine, valsartan, and statin medication). To strengthen the participant selection process, patients who passed all of the inclusion criteria but didn't have any of the exclusion criteria were then confirmed using the GAD65 assay.[9] The nutritional status of children aged 10 – 19 was determined by charting their body mass index (IMT) on a standardized WHO chart and then categorizing them as obese, overweight, normal, or underweight.

2.2 HbA1c Variability

Long-term glycaemic variability is based on HbA1c examinations, which are taken six times during patients' check-up control at the outpatient clinic. Each examination was calculated by implementing the coefficient of variation (HbA1c-CV), standard deviation (HbA1c-SD), and HbA1c Variability Score (HVS).

2.3 Measurement of CIMT

CIMT measurements were conducted using a Philips echocardiography machine equipped with an L12-5 linear transducer probe. The measurements were taken at the end-diastolic phase. Gain compensation must be modified when the number of CIMT readings is found at 60 dB or above. The neck veins were first presented in cross-section with the common carotid artery in the screen's center. When the transducer is rotated clockwise into the longitudinal plane, the common carotid artery is exhibited in its entirety according to the transducer trace. When near and far wall CIMT could be observed throughout the artery, and there was at least a clear 10 mm margin in the target segment, the transducer was perfectly positioned in reference to the common carotid artery. The transducer was tilted in the anterolateral and lateral view orientations to get the most representative and unambiguous CIMT border. The carotid artery should be oriented perpendicular to the path of the ultrasound beam, and the carotid bulb area should be visible on the left side of the image display for orientation purposes to detect the CIMT boundary clearly. For analysis, digital loops from two distinct scan angles must be acquired and stored. The right and left Common Carotid Artery (CCA), carotid bulb, and internal carotid arteries were all tested for CIMT. The CIMT data is collected and evaluated to determine the average CIMT value (mean CIMT).[10,11] In childhood, the normal average general CIMT value is less than 0.5 mm.8

2.4 Measurement of FMD

The FMD response of the brachial artery was measured using a Philips echocardiography machine equipped with a high-resolution L12-5 linear transducer probe. On the forearm, a blood pressure cuff is placed. A longitudinal scan of the brachial artery is performed 5 to 10 cm below the elbow. To ensure picture consistency, the transducer was positioned in the same area as the clearest B-mode image of the front and posterior intima interfaces between the lumen and the vessel wall. The depth and gain settings have been adjusted to maximize the picture of the arterial lumen wall interface. After obtaining a baseline longitudinal image for 30 seconds, the cuff blood pressure was increased to 50 mm Hg above the systolic pressure and maintained for 5 minutes. For up to three minutes after the cuff was deflated, continuous longitudinal images of the arteries were taken. The direct brachial artery diameter change was expressed as a percentage change compared to the diameter of the artery before cuff inflation. FMD was computed by comparing the peak vessel diameter at baseline to the percentage change in peak vessel diameter. The FMD percentage is calculated by multiplying [(peak diameter - baseline diameter)/baseline diameter] by 100%. The normal value for FMD in childhood is more than 8.3%.[12]

2.5 Statistical Analysis

All data were analyzed using SPSS version 22. P-value < 0.05 was considered statistically significant. Categorical variables were compared using the x2 or Fisher's exact test, while continuous variables were compared using the Student's t-test or the Mann–Whitney test. Logistic regression analyses were used to identify variables with a P-value 0.25 in the univariate study as independent predictors of MACE. Receiver operating characteristic (ROC) curves were developed to determine the cutoff threshold for LAEF as MACE predictors. Survival analysis were analyzed using the Kaplan–Meier technique and the log-rank test. Decrease of functional capacity in 6 month and 12 month compared between 2 groups (base of cut off point of LAEF) and analyzed using x2.

3. Results

3.1 Characteristics of research subjects

We enrolled 82 subjects with T1DM with a mean age of 13.28 ± SD 4.32 years old. The HbA1c variability study was conducted using three different variables: the HbA1c variability score (HbA1c Variability Score/HVS), the HbA1c standard deviation (HbA1c-SD), and the HbA1c coefficient of variability (HbA1c-CV). The mean CIMT value found in overall patients was 0.47 mm (SD 0.11 mm), while the mean FMD value was 0.16 (SD = 0.16). Table 1 summarizes the characteristics of the subjects in this study.

Table 1. Characteristic data of all subjects.

Variable		Total (n=82)	
		n/mean	%/SD
Demography		13.28	4.32
	Age		
	Gender	37	45.1
	Man	45	54.9
	Woman	18.45	4.17
	BMI (kg/m2)	111.67	9.782
	Systole (mmHg)	73.9	4.806
	Diastole (mmHg)		
Biomarker			
	Ureum (mg/dL)	21.7805	9.4145
	Creatinine (mg/dL)	0.5929	0.2798
	SGOT (U/L)	33.05	4.716
	SGPT (U/L)	32.89	4.751
	HDL (mg/dL)	56.57	13.24
	LDL (mg/dL)	114.32	34.196
	TG (mg/dL)	101.71	42.23
	Total Cholesterol (mg/dL)	168.91	37.11
	Hb (g/dL)	14.11	1.22
	WBC (103/μL)	8.27	2.76
HbA1C Variability			
	HVS	43.90	34.14
	HbA1c-SD	0.78	0.71
	HbA1c-CV	0.086	0.076
IMT (mm)		0.47	0.11
FMD		0.16	0.16

Note. BMI = Body mass index; SGOT = Serum Glutamic Oxaloacetic Transaminase; SGPT = Serum Glutamic Pyruvic Transaminase; HDL = High-density lipoprotein; LDL = low-density lipoproteins; TG = Triglycerides; HVS = HbA1c variability score; FMD = Flow-Mediated Dilation.

Table 2. Characteristics in groups with normal and abnormal CIMT

Characteristic	CIMT value < 0.5 mm (n = 53)	CIMT value > 0.5 mm (n = 29)	p
Age	11.57 ± 4.190	16.41 ± 2.51	0.000*
BMI	18.86 ± 3.88	17.69 ± 4.68	0.232
Gender			
Man	43.40%	48.30%	0.847
Woman	56.60%	51.70%	
Lipid Profile			
total cholesterol	85.04 ± 28.52	96.69 ± 37.53	0.118
TG	98.85 ± 42.56	1.07 ± 42.59	0.414
HDL	56.83 ± 13.39	56.10 ± 13.43	0.815
LDL	1.06 ± 36.08	1.21 ± 28.32	0.041*
HbA1C index	9.29 ± 2.45	10.24 ± 2.11	0.084
HbA1c Variability			
HVS	33.58 ± 34.81	62.76 ± 24.33	0.000*
HbA1c-SD	0.64 ± 0.77	1.15 ± 0.68	0.005*
HbA1c-CV	0.08 ± 0.08	0.10 ± 0.06	0.137

Note. *) significant if the p-value is 0.05 or lower

Table 2 demonstrates a considerable age difference between the two groups., with a p = 0.000. There was also a significant difference in the LDL variable (p = 0.041) but no significant difference in the other lipid variables. There were significant variations in HbA1c variability values, namely the HVS value with p = 0.000 and the HbA1c-SD value with p = 0.005.

According to Table 3 below, there was a significant difference in age between the FMD groups, with a p-value of 0.010. There was also a significant change in the LDL variable with a p-value of 0.027 but no difference in the other lipid profiles. There were significant changes in HbA1c variability between the FMD groups, specifically the HVS value (p = 0.000), HbA1c-SD (p = 0.001), and HbA1c-CV (p = 0.002). There was also a significant difference between the groups in terms of HbA1c index value, with a p-value of 0.030.

Table 3. Characteristics in groups with normal and abnormal FMD

Characteristic	FMD value < 8.3% (n = 36)	FMD value > 8.3% (n = 46)	P
age	14.58 ± 2.802	12.26 ± 5.048	0.010*
BMI	17.85 ± 4.47	18.92 ± 3.95	0.257
Gender			
Man	41.70%	47.80%	0.739
Woman	58.30%	52.20%	
Lipid Profile			
total cholesterol	1.77 ± 36.98	1.63 ± 36.78	0.084
TG	94.08 ± 36.15	85.30 ± 28.68	0.233
HDL	57.67 ± 13.09	55.72 ± 13.59	0.514
LDL	1.20 ± 31.79	1.04 ± 34.47	0.027
HbA1C index	10.26 ± 2.65	9.13 ± 2.01	0.030*
HbA1c Variability			
HVS	65.56 ± 24.19	26.96 ± 31.61	0.000*
HbA1c-SD	1.08 ± 0.84	0.54 ± 0.49	0.001*
HbA1c-CV	0.12 ± 0.09	0.06 ± 0.05	0.002*

Note. *) significant if the p-value is 0.05 or lower

Correlation analysis using Spearman's Rank test was performed on all subjects to assure the association between lipid profile and FMD (Table 4). There was no significant correlation found among HDL (ρ=-0.029; p=0.796), LDL (ρ=-0.213; p=0.055), TG (ρ=-0.179; p=0.107), total cholesterol (ρ= -0.182; p= 0.101), and FMD in this test. There was no significant correlation among HDL (ρ=-0.042; p=0.707), TG (ρ=0.170; p=0.126) with IMT. There was a positive correlation between LDL (ρ = 0.318; p = 0.004) and total cholesterol (ρ= 0.230; p = 0.038) with IMT.

HbA1C variability as determined by HVS had a significant negative correlation coefficient value ((ρ)=-0.498 (p=0.000; p0.05)) in all subjects, as well as in HbA1c-SD (ρ=-0.467; p=0.000) and HbA1c-CV (ρ=-0.400; p=0.000) to FMD levels. Additionally, a significant positive correlation coefficient value was discovered between IMT and the value of HbA1c variability utilizing HVS (ρ=0.455; p=0.000), HbA1c-SD (ρ=0.434; p=0.000), and HbA1c-CV (ρ=0.325; p=0.003).

Table 4. Spearman's Rank Test correlation test results.

Spearman's Rank Test	Dependent variables			
	FMD		IMT	
	rho (ρ)	P	rho (ρ)	P
BMI	-0.018	0.87	-0.084	0.453
Independent variables				
Lipid Profile				
HDL	-0,029	0,796	-0,042	0,707
LDL	-0,213	0,055	0,318	0,004*
TG	-0,179	0,107	0,170	0,126
total cholesterol	-0,182	0,101	0,230	0,038*
HbA1c Variability				
HVS	-0,498	0,000*	0,455	0,000*
HbA1c-SD	-0,467	0,000*	0,434	0,000*
HbA1c-CV	- 0,400	0,000*	0,325	0,003*

Note. *) significant if the p-value is 0.05 or lower

According to Table 5, the correlation coefficient (R) for the lipid profile (R=0.374) is less than the variability of HbA1c (R=0.410) in its effect on FMD. Similarly, for IMT, HbA1c variability (R=0.557) had a more significant impact than lipid profile variability (R=0.320). LDL levels exhibited a more substantial effect on FMD (R=0.316) and IMT (R=0.268) than other lipid profiles. HVS had a more significant impact on FMD (R=0.398) and IMT (R=0.468) than different HbA1c variations.

HVS (R=0.398), LDL (R=0.316), and HbA1c-SD (R=0.293) were the three most influential variables on FMD. HVS (R=0.468), LDL (R=0.268), and total cholesterol (R=0.198) were the three most impactful variables on IMT. It is known that the combination of lipid profile and HbA1c fluctuation contributes 25.1 % to FMD using this model. Meanwhile, the lipid profile and HbA1c variability together accounted for 34.5 % of the variance in IMT.

Table 5. Linear regression test results.

Variable	Dependent variables			
	FMD		IMT	
	R	R^2	R	R^2
Lipid Profile	0.374	0.140	0.320	0.102
HDL	0.020	0.000	0.080	0.006
LDL	0.316	0.100	0.268	0.072
TG	0.242	0.059	0.143	0.020
total cholesterol	0.268	0.072	0.198	0.039
HbA1c Variability	0.410	0.168	0.557	0.310
HVS	0.398	0.158	0.468	0.219
HbA1c-SD	0.293	0.086	0.185	0.034
HbA1c-CV	0.263	0.069	0.101	0.010
Total	0.501	0.251	0.588	0.345

Note. *) significant if the p-value is 0.05 or lower

4. Discussion

This study aims to determine the long-term relationship of glycaemic variability by utilizing the formula of HbA1c variability from some HbA1c examinations and lipid profile examinations consisting of total cholesterols, triglycerides, HDL, and LDL; towards the CIMT and FMD values. The study revealed that the result of HbA1c variability and lipid profiles was associated with the increase in IMT thickness and the decrease in FMD percentage.

Blood sugar control must be managed adequately in patients with T1DM to avoid or minimize the risk of complications. This study demonstrated that when blood sugar regulation is less than optimal, there would be a risk of early endothelial dysfunction, which accelerates the progression of atherosclerosis. Other studies have shown a correlation between high HbA1c variability values, a reduction in clinical symptoms, and consequences that manifest early in patients with diabetes.

HbA1c is a test that can be used to determine the average exposure to blood sugar over two to three months, including the increase in postprandial blood sugar. It has a low intra-individual variability and has been used to examine long-term diabetes control. However, as indicated by a study in which long-term glycaemic variability corresponds with either the average blood glucose concentration (r=0.73) or the average HbA1c value (r=0.55), long-term glycaemic variability exams may better reflect hyperglycaemic situations.[13]

Long-lasting fluctuations in blood sugar levels contribute to the establishment of early microvascular problems in patients with T1DM. Kilpatrick et al. showed that HbA1c fluctuation might be beneficial in predicting nephropathy and diabetic retinopathy later in life.[14] The Finnish Diabetic Nephropathy (Finn Diane) observational study demonstrated that glycaemic variability as measured by the standard deviation of serial HbA1c examinations from baseline to follow-up could be used to predict the development of kidney disease in T1DM patients.[15] Hsu et al. found that long-term glycaemic fluctuation was independently linked with the frequency of microalbuminuria problems in a cohort with T2DM.[16] Additionally, a meta-analysis revealed an association between long-term HbA1c fluctuation in patients with T1DM and renal disease (risk ratio 1.56 (95 percent confidence interval [CI] 1.08–2.25)), cardiovascular disease (1.98 (1.39–2.82)), and retinopathy (2.11 (1.54–2.25; 2.89)).17 Additionally, another meta-analysis study revealed that younger patients with T1DM had a high IMT (mean difference (d) = 0.03, 95% confidence interval (CI) = 0.02-0.04).[18] The results of this study indicate that long-term HbA1c fluctuation is connected with the progression of vascular damage caused by endothelial dysfunction, as seen by the lower proportion of FMD values and higher IMT values, which is consistent with earlier research.

Other studies have also demonstrated the influence of HbA1c fluctuation on IMT. It is connected with a drop in IMT value, which is then viewed as a clinical outcome of cardiovascular disease problems, according to meta-analysis research of Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) (CVD). CVD complications were reduced in patients with low blood sugar fluctuation and a lower IMT than in those with high blood sugar variability. By lowering the value of glycaemic variability, it is possible to improve insulin resistance and IMT, reducing the risk of cardiovascular disease.[19]

The standard deviation has long been employed to quantify variability, even though SD is a measure of dispersion rather than actual variability. SD has been found to have a linear correlation with mean glucose levels. When the standard deviation is reduced by the mean and a coefficient of variation is calculated, the linear link is mainly eliminated. However, Buscemi et al. investigated glycaemic variability using the coefficient of variation obtained from continuous blood glucose monitoring. They discovered a high correlation between the coefficient of variation in glucose and endothelial dysfunction and atherosclerosis in non-diabetic participants. Another study by Wei et al. demonstrated a substantial correlation between long-term HbA1c fluctuation and endothelial and renal impairment in the T2DM group.[19]

Oxidative stress is a significant contributor to endothelial cell damage. Numerous earlier research has demonstrated that changes in blood glucose levels caused by oxidative stress can have a detrimental effect on organ cells. The sources and targets of oxidative stress during blood sugar variations have been identified. Along with the NADPH oxidase and AKT pathways, mitochondria play a critical role in producing superoxide during glycaemic fluctuation. Additionally, glycaemic variability contributes to increased chromatin remodeling, which plays a crucial role in the metabolic memory established by glycaemic variability.[7] Another investigation in the T2DM group demonstrated that chromatin modifications were responsible for persistent vascular impairment.[20]

On average, women have more excellent endothelial vasomotor activity than men. Numerous causal hypotheses were proposed; one of them was that women have a smaller body surface area (BSA), a lower body mass index (IMT), and a smaller brachial artery baseline diameter. Estrogen has been shown to increase endothelium function in prepubescent subjects.[21] There was no significant difference in FMD levels between the groups of male and female subjects in this investigation. This is related to various factors, including the duration of T1DM disease, glycaemic fluctuation, and lipid profile abnormalities.

4.1 Correlation between lipid profiles and FMD and IMT

Insulin usually plays a critical function in the regulation of lipid metabolism. Insulin inhibits the hormone-sensitive lipase found in fat tissue. Insulin inhibits the adipose tissue's release of free fatty acids (FFA). Insulin also has a significant effect on postprandial lipid metabolism by lowering chylomicron formation and boosting Lipoprotein Lipase (LPL) activity, accelerating chylomicron catabolism.[22]

As a result of insulin, the liver's ability to synthesize VLDL is reduced, and LDL catabolism is increased. Processes of varying degrees of complexity. A rise in LDL cholesterol, non-HDL cholesterol, and triglycerides of 0.103, 0.129, and 0.052 millimoles per liter was associated with every 1% increase in HbA1c in the Coronary Artery Calcification in Type 1 Diabetes (CACTI) trial. This indicates that hyperglycemia plays a significant role in developing lipid abnormalities in T1DM patients.[22] Another cross-sectional study in a group of young patients with T1DM (SEARCH for Diabetes in Youth) established that patients with uncontrolled HbA1c have a higher lipid profile value than the normal group and that atherogenic changes in lipoprotein composition occur even in patients with a short duration of T1DM disease.[23]

An observational study of patients with T1DM in Sweden found that every 1 mmol/l increase in LDL cholesterol increases the risk of cardiovascular complications by 9% in patients who do not receive lipid-lowering drug therapy. However, this study demonstrates that LDL levels cannot be used as a good marker for cardiovascular risk in patients with T1DM undergoing primary prevention. The EURODIAB Prospective Complications Study in patients with type 1 diabetes similarly confirmed this.[24] However, the ADA guideline states that LDL values of more than 2.6 mmol/l in diabetes people are indicative of elevated cardiovascular risk.[25]

Some studies have demonstrated that patients with T1DM with poor blood sugar control would tend to have higher LDL cholesterol levels than patients with T1DM with normal blood sugar control. Triglyceride and other lipoprotein levels will likewise decline and return to normal. Plasma PCSK9 levels, which are involved in the metabolism of LDL, will again increase and correlate with HbA1c levels. Plasma HDL cholesterol levels will also rise in people with well-controlled T1DM. Plasma HDL cholesterol levels will also be normal and may even increase in people with well-controlled T1DM. Increased HDL cholesterol cannot be claimed to be atheroprotective, as the HDL particles found in Patients with T1DM do not substantially demonstrate this.[22] Additionally, LDL can exacerbate inflammatory reactions by engaging the natural immune system via the Toll-like receptor (TLR) pathway, stimulating pro-inflammatory signals. Through this TLR, the presence of cholesterol crystals, the trapping of extracellular neutrophils, and hypoxic conditions activate the inflammasome encoded by the nucleotide-binding leucine-rich repeat-containing pyrine receptor (NLRP3) found in the cytoplasm of macrophages found in the intima layer of arteries. The inflammatory process, including inflammation of endothelial cells, is facilitated by the inflammasome. This complex protein plays a role in producing pro-inflammatory cytokines such as IL-1 and IL-18.[26] One study showed an increase in LDL was associated with an increase in cIMT.[27] Another study likewise demonstrated the same thing, demonstrating that an increase in LDL is a major predictor of progressive increases in CIMT.[28] This was demonstrated in this study by the increased value of LDL, resulting in a higher IMT score.

Hyperglycaemia accelerates the oxidation of LDL, particularly in patients with uncontrolled T1DM. Oxidized LDL has the potential to become atherogenic, forming foam cells and progressing to atherosclerosis. Uncontrolled T1DM will increase HDL triglycerides. Glycation of apoA-I occurs in HDL as well, impairing HDL function. Additionally, the presence of pro-inflammatory proteins in HDL, such as serum amyloid A, impairs HDL's atheroprotective effect. Proteomic analysis of young Patients with T1DM revealed a shift in the composition of HDL proteins but no evidence of an increased risk of cardiovascular disease problems later in life.[22]

Although blood sugar levels of patients with T1DM were effectively controlled, a qualitative examination of their lipid profile revealed aberrant lipoproteins, indicating that this disorder has the potential to become atherogenic later in life. According to the study, tiny VLDL induced by peripheral hyperinsulinemia conditions decreased plasma FFA levels and activated LPL and VLDL catabolism in managed T1DM patients. A higher free cholesterol/lecithin ratio in peripheral VLDL decreases its fluidity and stability. Additionally, the peripheral circulation increased in small dense triglyceride-rich LDL and small dense LDL particles. LDL particles having a low density are related to an increased risk of cardiovascular disease.[22] In this study, the duration of T1DM disease is determined by the patient's age; the older the patient, the higher the IMT value and the lower the FMD percentage. Small dense LDL accumulating in the peripheral circulation over time will trigger a protracted inflammatory response, resulting in continued endothelial dysfunction and atherosclerosis even after the patient's blood sugar levels are reduced.

In patients with T1DM with adequate blood sugar control, insulin increases lipoprotein lipase regulation, resulting in a more remarkable synthesis of tiny HDL particles than in normal settings. Because HDL cholesterol is not physiologically elevated in diabetic individuals, there has been HDL dysfunction in this scenario, where high HDL concentrations do not give a protective impact against cardiovascular risk.[28] According to a study, the value of HDL begins to lose its protective impact above 1.3 mmol / l in women, with high HDL cholesterol levels associated with an increased risk of cardiovascular disease in both men and women.[29]

Chronic inflammatory problems common in patients with T1DM would alter lipid metabolism as well, both in the regulation route of inflammatory reactions via the innate and adaptive immune systems. This is due to the pro-inflammatory cytokines' method of action, which affects fatty acid oxidation and can activate lipoprotein lipase in muscle and adipose tissue, as well as hepatic lipase, resulting in dyslipoproteinemia. This creates a vicious circle in which the inflammatory process affects lipid metabolism and vice versa, hastening the progression of atherosclerosis.[22]

5. Conclusion

Variability of HbA1c and lipid profile (LDL and total cholesterol) has effects on increasing the CIMT levels and decreasing the FMD of the brachial artery in children with T1DM.

6. Declarations

6.1. Ethics Approval and Consent to participate
This study was approved by local Institutional Review Board, and all participants have provided written informed consent prior to involvement in the study.

6.2. Consent for publication
Not applicable.

6.3. Availability of data and materials
Data used in our study were presented in the main text.

6.4. Competing interests
Not applicable.

6.5. Funding source
Not applicable.

6.5. Funding source
Not applicable.

6.6. Authors contributions
Idea/concept: DAI, CT. Design: DAI. Control/supervision: CT, NK, SW, VYSP. Literature search: CT, NK, SW, VYSP. Study quality assessment: CT, NK, SW, VYSP. Data extraction: DAI. Statistical analysis: DAI. Results interpretation: DAI. Critical review/discussion: CT, NK, SW, VYSP. Writing the article: DAI. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

6.7. Acknowledgements
We thank to Brawijaya Cardiovascular Research Center.

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